

Quick guide

The unfolded protein response

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Where does the UPR function?

Between the endoplasmic reticulum (ER) and the nucleus of eukaryotic cells. All secreted proteins and proteins that reside in secretory compartments translocate as nascent peptide chains into the ER, where they may undergo folding, modification and assembly before assuming their functional conformations. The ER maintains a specialized oxidizing environment to aid chaperones and other components to promote disulphide bonding, glycosylation, folding and assembly. The ER also mediates protein quality control to ensure that only properly folded proteins exit the ER.

What is the UPR? UPR signaling is triggered when the protein-processing capacity of the ER is exceeded by the current demand. In yeast, it results in the transcriptional upregulation of more than 300 genes encoding ER chaperones (e.g., BiP, calreticulin, calnexin), protein-folding enzymes (e.g., PDI, FKB2), regulators of phospholipid metabolism, and proteins involved in degrading permanently misfolded proteins.

How are unfolded proteins in the ER lumen sensed by the UPR? In yeast, the only known UPR sensor is IRE1, a type I ER transmembrane receptor kinase/endoribonuclease. IRE1 senses ER protein folding needs through its luminal domain. Prior to UPR activation, IRE1 is held in a monomeric conformation by BiP (a major ER chaperone) bound to its luminal domain. Rising levels of unfolded proteins cause BiP dissociation, leading to IRE1 oligomerization and kinase activation. Activated IRE1 then functions as the site-specific endoribonuclease responsible for cleaving a unique intron from *HAC1*

mRNA (*XBP1* mRNA in mammals). The resulting spliced form of *HAC1* mRNA (and *XBP1*) encodes a potent UPR-specific transcription factor critical for upregulating UPR target genes.

How is ER stress sensed in higher eukaryotes? In addition to IRE1, higher eukaryotes utilize two additional sensors, the ER transmembrane kinase PERK and the ER transmembrane transcription factor ATF6 (Figure 1). Both proteins are activated in a manner similar to IRE1 following the dissociation of BiP bound to their ER luminal domains. In the case of PERK, BiP dissociation promotes phosphorylation of its substrate, the translation initiation factor eIF2 α , at serine 51, resulting in inhibition of translation. In the case of ATF6, BiP release promotes ATF6 translocation to the Golgi where an active transcription factor fragment is produced and translocates to the nucleus.

What are the consequences of activating UPR? In addition to transcription of the UPR target genes and a decrease in protein translation, UPR activation produces a transient cell-cycle arrest at G1/S in higher eukaryotes. From this resting point, cells may adapt successfully to the impending stress or commit to apoptosis.

What physiological events trigger UPR pathway activation? The best studied example of UPR

activation in a physiological event is during the maturation of resting B cells into immunoglobulin-secreting plasma cells, a process in which IRE1-mediated splicing of *XBP1* mRNA has been shown to be a critical event. In addition, an important role for UPR signaling in the insulin-secreting pancreatic β cells is suggested by a genetic link between PERK and a certain type of juvenile diabetes.

What remains to be discovered? Many things, such as the molecular events leading to BiP dissociation from UPR sensors, the mechanism of UPR downregulation, and the potential links between ER protein load and levels of ER membrane phospholipids.

Where can I find out more?

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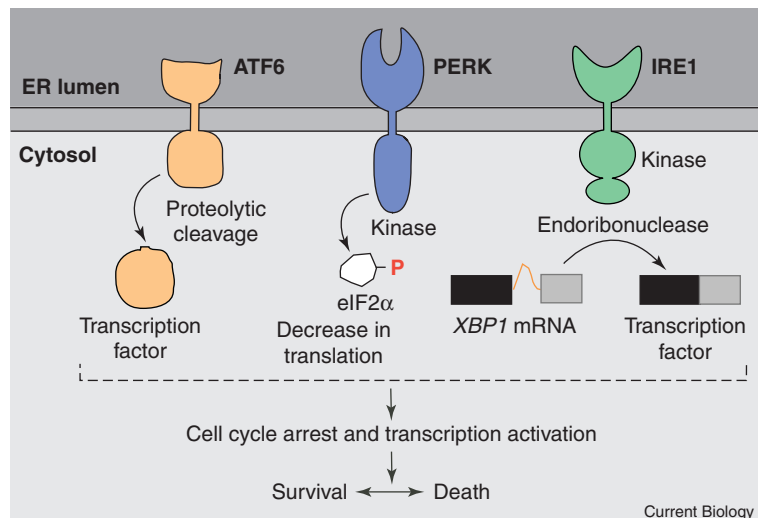


Figure 1. The UPR in higher eukaryotes. See text for details.